BLOOD PRODUCTS ADVISORY COMMITTEE MEETING
67th MEETING – September 14-15, 2000

TOPIC: HIV p24 antigen testing of plasma for fractionation - Potential Criteria for Discontinuation

Issue: Should FDA permit manufacturers of plasma derivatives to replace HIV p24 antigen testing with a licensed minipool NAT method that has equal or greater sensitivity ?

Background

Introduction:

During the past decade there has been a dramatic reduction in the transmission of HIV by blood and blood products primarily due to the implementation of sensitive tests for viral antibody, antigen, and nucleic acid and, in the case of plasma derivatives, the use of effective virus removal and inactivation methods for plasma derivatives. The major sources of remaining risk are window period donations, viral variants, atypical seroconversion and laboratory testing error. According to recent reports, donations during the window period constitute at least 90% of the risk. Therefore, measures to close the window period could further reduce the low residual risk in HIV transmission by blood and plasma. In 1994, FDA held a workshop to discuss the potential application of nucleic acid based methods to donor screening for HIV. It was felt at the time that although these methods were clearly sensitive, they were not ready for implementation on a large scale. It was subsequently decided in 1996 that p24 antigen (Ag) testing could be adopted as an interim measure for interdicting window period donations until more sensitive methods become available. Despite the effectiveness of viral clearance and inactivation procedures in the manufacture of plasma derivatives, FDA recommended donor testing for HIV-1 p24 antigen for plasma for fractionation as an added safeguard. Such testing limits the virus burden that may be present in a plasma pool for fractionation.

Subsequent to implementation of HIV p24 Ag testing in 1996, the industry actively pursued development of nucleic acid testing (NAT) for screening blood and plasma donors. Due to the cost and labor intensity of NAT there was much interest in testing minipools of plasma and by 1997, some manufacturers in Europe had voluntarily instituted NAT on minipools. At about that time, the European Union had issued a directive that by July 1,1999 HCV RNA testing would be required in Europe for all plasma for fractionation and that the requirement for HIV-1 RNA testing would follow at a later date. In the U.S., testing of minipools first was introduced as an in-process control test for plasma for fractionation. However, the FDA position to regard pooled sample testing by NAT as a form of donor screening and the European directive which applied to both Source and Recovered Plasma provided impetus to the rapid development of NAT for all blood and plasma donations. FDA has taken the position that all NAT tests used to

screen blood and plasma are subject to regulation as biological products under the licensing mechanism. Since NAT screening of donors was expected to improve blood safety while not interfering with current measures of safety, FDA permitted the clinical study of this investigational technology on a large scale. Such large scale studies would be necessary to demonstrate the efficacy of NAT primarily because the frequency of window period donations is low. At the present time virtually all Source Plasma and Whole Blood collected in the U.S. is being tested by a minipool NAT method for HCV and HIV-1 under an approved IND. FDA has not yet licensed a NAT method for use in screening of donor blood and plasma, including Source Plasma.

Criteria for discontinuation of HIV p24 Ag and replacement by minipool NAT

With the implementation of NAT for detection of window period donations, the question of replacing HIV p24 Ag testing by NAT has been raised by many investigators. Since both tests are for direct makers for the virus, it has been suggested that it may be feasible to replace p24 Ag on the neat sample with minipool NAT if it is found to be of equal or greater sensitivity. At the Blood Products Advisory Committee (BPAC) meeting held in March 1999, FDA defined criteria for discontinuation of HIV p24 Ag and replacement by minipool NAT. To summarize briefly, the following criteria were presented:

a. The sensitivity of the NAT method should be equal to or greater than that of p24 Ag testing for the window period. This could be established by testing all available and properly stored repository specimens that are p24 Ag positive and antibody negative and commercially available serconversion panel specimens in the pooled NAT method and neat p24 Ag method.

b. The frequencies of NAT and p24 Ag positivity in Ab positive and negative specimens should be evaluated in prospective studies.

c. NAT and p24 Ag should have equivalent sensitivity for the major HIV-1 subtypes. NAT should detect all variant subtypes detected by p24 Ag tests.

d. Weakly reactive p24 Ag positive specimens should be reproducibly detected by the NAT method on multiple days by multiple operators and for multiple kit lots, and instruments

FDA also indicated that the NAT method would have to be licensed before it could be used to replace the antigen test. FDA has published guidance on the validation of NAT methods to screen plasma donors. Among the major considerations for the sensitivity of NAT on pools is the analytical sensitivity of the NAT method on the pool and the original donation, as well as the pool size tested. FDA has defined a proposed sensitivity limit of 100 copies/ml for the pool test and 5,000 copies/ml for the original donation. FDA has not specified pool size limits, thereby allowing manufacturers to set these limits based on the analytical sensitivity of their specific test. Source Plasma donations are currently being tested in pools ranging from 96 to 1200 donations.

To establish sensitivity criteria whereby p24 Ag can be discontinued, it is important to understand the early dynamics of HIV infection and to establish a relationship between detectable levels of viremia by p24 Ag vs. minipool NAT. Recent data indicate, that in studies where 146 serial specimens from 43 HIV plasma donor panels were characterized by tests for HIV RNA , p24 Ag and HIV Ab, the viral load at the time of p24 antigen seroconversion was estimated at 10,000 copies/ml (CI = 1,000 – 100,000). Therefore a NAT method should be able to detect a minimum of 10,000 copies/ml in order to replace currently licensed p24 Ag tests. For example, if a NAT method has a test sensitivity of 100 copies/ml the maximum pool dilution where p24 antigen and NAT would be expected to have equal sensitivity is 100 samples/pool. However, if a test has a higher analytical sensitivity e.g. 10 copies/ml, it is conceivable that a pool size of 1,000 would also permit equal sensitivity of NAT and p24.

In regard to plasma for further manufacture, it is important to note that viral inactivation methods provide an added measure of safety. Since the end of 1987 there have been no transmissions of HIV by albumins, immuneglobulins , AHF or F IX. Heat treatment used in albumin production can inactivate the infectivity of HIV-1 by at least 7 logs which is three logs more virus than the maximum concentration reported in the plasma of infected individuals (10^4 infectious doses/ml). The Cohn-Oncley method used to manufacture immuneglobulins can remove greater than 10^{15} infectious doses of HIV per ml which is at least 11 logs greater than the maximum circulating infectious doses per ml. Finally, there have been no seroconversions to anti-HIV among hemophiliacs who have received AHF or F IX manufactured from screened plasma and that has been virally inactivated.

Based on the rationale and criteria outlined above, the FDA is seeking the recommendations of the BPAC on the potential discontinuation of HIV p24 antigen testing and replacement by a NAT method for plasma collected for fractionation. As outlined above, the two major considerations are: a) that a NAT test is of equal or greater sensitivity than the p24 Ag test, and b) that viral removal/inactivation methods validated to remove/inactivate circulating levels of HIV detected by p24 or NAT are in place for plasma collected for further manufacturing.

Questions for the Committee:

1. Do the Committee members agree that HIV-1 p24 antigen testing of Source Plasma may be discontinued if:

    a) It is demonstrated that a particular licensed NAT method can detect HIV at a level of 5,000 copies/ml or less in a unit of plasma, even if the donor sample is tested as part of a pool, and
    b) Comparative studies of the NAT method vs. HIV-1 p24 are consistent with the hypothesis that the NAT method is of equal or greater sensitivity (including the ability to detect major subtypes) ?

2. If committee members disagree, please comment on an appropriate alternative.